The Effects of NSAIDs on the Bone Healing Process

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Hypothesis: COX-2 inhibiting NSAIDs slow down the bone healing process

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are anti-inflammatory pain relievers and are the most common pain relievers consumed. Most NSAIDS can be bought over-the-counter (OTC) and can be taken with minimal side effects. These most commonly include include aspirin, ibuprofen (Advil or Motrin), and naproxen (Aleve). Patients are aware of the side effects that come with the prescription forms of drugs because doctors are required to inform their patients. However, those who buy OTC drugs are not usually aware of the effects because there is no medical advisor present to inform them. One side effect that is not currently relayed, is the adverse effect of NSAIDs on the bone healing process. This study evaluates the mechanisms and roles that NSAIDs take on during the stages of the bone healing process after an injury and their correlation, by analyzing the pathway of NSAIDs in the body. Through investigation and statistical analysis of many peer-reviewed academic papers, this study concludes NSAIDs slow down the bone healing process and warrants further research in this field.

Introduction

NSAIDs are Non-steroidal Anti-inflammatory Drugs and are taken for the purpose of reducing pain and inflammation in individuals with muscular and skeletal pain, arthritis, menstrual cramps, and headaches. They work by blocking the production of an enzyme called cyclooxygenase (COX). Prostaglandins are hormone-like substances that are required for inflammation throughout the body. They are formed from a poly-unsaturated fatty acid called arachidonic acid. COX enzymes are what catalyze the transformation of arachidonic acid into prostaglandins. NSAIDs block the formation of the COX enzymes and therefore reduce inflammation throughout the body.

The COX enzymes can be found in two different forms: COX-1 and COX-2. COX-1 is invariably expressed by the body while COX-2 must be activated by an offending factor in order to be induced for production.

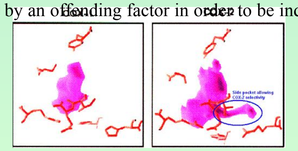


Figure 1: The only difference between COX-1 and COX-2 is an additional amino acid side-pocket on COX-2.

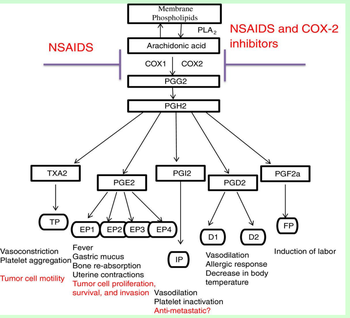


Figure 2: The pathway of arachidonic acid, showing how NSAIDs block COX and how PGs interact in the body.

COX is produced by proinflammatory cytokines and at the sites of inflammation (1). COX-2 is produced more abundantly during initial bone repair after an injury as tissue damage is present and therefore more cytokines are present. COX-2 allows for the production of a prostaglandin called PGE2. PGE2 is required for the homeostasis of osteoblasts and osteoclasts, two different types of bone cells. This is called bone reabsorption (2). This process maintains bone health and is required for bone healing. Since NSAIDs reduce inflammation by blocking the production of COX enzymes, the process of turning arachidonic acid into PGE2 is inhibited. With the consumption of selective NSAIDs, this process is able to continue, as COX-1 is still present. However, when non-selective NSAIDs are consumed for the purpose of reducing inflammation due to a bone deformation, the entire cycle of PG production needed for bone resorption is stopped, due to the fact that the inhibition of the COX enzymes.

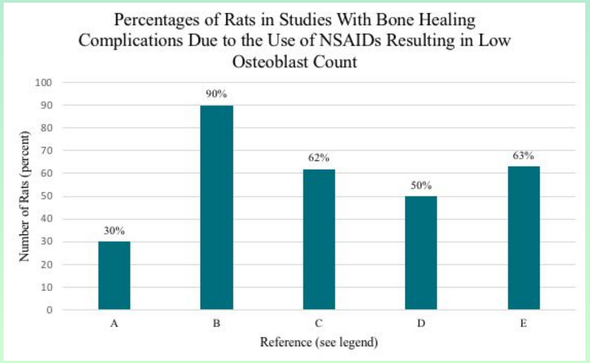
Purpose

The purpose of this study was to investigate the process of NSAID interaction in the body and their role in the bone healing process.

Methods

-Collection of peer-reviewed, academic articles
-Systematic review of related studies and articles
-Collection of data from related studies
-Writing of academic paper
-Statistical analysis of data

Results



A: P. E. Persson, G. Sisask, and O. Nilsson, 2005
B: E. Sudmann and G. Bang, 1979.
C: H. L. Allen, A. Wase, and W. T. Bear, 1980
D: T. Karachalios, L. Boursinos, L. Poultsides, L. Khaldi, and K. N. Malizos, 2007
E: K. D. Riew, J. Long, J. Rhee et al., 2003

Figure 3: The average percentages of rats out of the studies referenced in the legend are displayed. The percentages compare rats with bone healing complications due to low osteoblast counts in different studies. The studies each compared osteoblast counts during healing in rats treated with NSAIDs and a placebo.

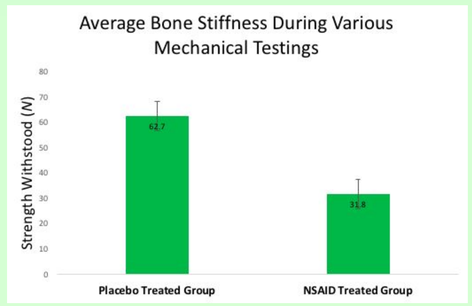


Figure 4: p=0.01; Averages of bone stiffness during various types of mechanical testing are shown (in newtons) on the y-axis, and the placebo and NSAID treated rat groups are displayed on the x-axis.

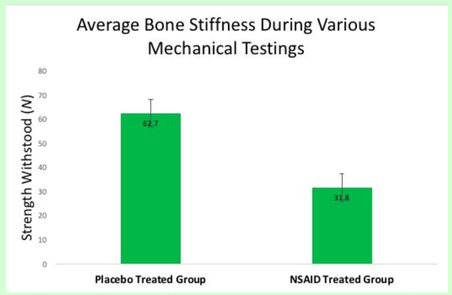


Figure 5: p=0.01; Averages of bone strength withstood during various types of mechanical testing are shown (in newtons) on the y-axis, and the placebo and NSAID treated rat groups are displayed on the x-axis.

In Figure 3, the average osteoblast count among all five studies was ≈180 cells per slide. Among the five NSAID-treated groups, an average of 74.75 osteoblasts was counted on each slide. In the placebo groups, an average of 172.75 osteoblasts was counted per slide. The outlier among the data set in Figure 3 is Reference A with an average of bone healing complications of 30%. By means of angulation measurement with a protractor, the placebo-treated group had an average of 62.7 *N* withstood. The NSAID treated group had an average of 31.8 *N* withstood. The Chi-squared value for this data is p=0.01. By measuring the angulation of the bone, stiffness can be calculated. The farther a bone can bend, the less dense it is. Bone density is crucial for adequate strength and function. A decrease in bone density is a sign of incomplete healing, ultimately relating back to a bone's osteoblast count. In Figure 4, a similar analysis was conducted. The average values of bone strength from 10 academic, peer-reviewed journals are presented. Bone strength is similar to bone stiffness but is tested by means of the three-point flexure test. It again is measured in *N*. The average strength of the placebo-treated group was 47.9 *N* and the average of the NSAID treated rats was 32.03 *N*. The chi-squared value of this data is p=0.01. The strength of a bone is also determined by osteoblast quantity. The higher the density, the more weight that can be withstood.

Discussion

As can be assumed through the molecular pathway of arachidonic acid (see Figure 1), the COX-1 and COX-2 enzymes are essential for the formation of prostaglandins. PGs give way to the pathways of the more specialized PGs that have essential receptors in all cells. Specifically, PGE2 binds to the EP2R and EP4R receptors which signal bone resorption to occur. Bone resorption is the homeostasis of bone, where osteoclasts break down bone cells into Ca2+ and return the mineral to the bloodstream and osteoblasts absorb the Ca2+ and contribute to the formation of bone matrices. When this process is inhibited due to an absence of COX enzymes, osteoclasts will continue to break down and absorb the calcium needed for the formation of new osteoblasts. This results in a lesser number of osteoblasts and therefore a decrease in bone density. This interpretation is related to the consumption of NSAIDs for the purpose of reducing inflammation and pain after a bone injury such as a complete breakage or fracture. New osteoblasts are required for the formation of a new bone matrix after an injury, in order to reunite the broken bone tissue. Since NSAIDs inhibit the COX enzymes, osteoblast formation is also hindered. In many studies that have investigated this performance and course, NSAIDs used for the purpose of reducing inflammation and pain have shown to have detriments on the bone healing process.

Conclusion

Due to the fact that NSAIDs block the production of the COX enzymes, specifically COX-2, this study concludes that NSAIDs do slow down or inhibit the bone healing process.

Further Work

Taking into consideration that arthritis patients and osteoporosis patients make up the highest population of NSAID consumers, and that their conditions relates with the homeostasis of osteoblasts and osteoclasts, I would like to further my research by bringing about awareness of this research and applying it to these patients.

Acknowledgements

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References

1. Warner, T. D., et al. "Nonsteroid Drug Selectivities for Cyclo-Oxygenase-1 Rather than Cyclo-Oxygenase-2 Are Associated with Human Gastrointestinal Toxicity: A Full in Vitro Analysis." *Proceedings of the National Academy of Sciences*, vol. 96, no. 13, 1999, pp. 7563–7568., doi:10.1073/pnas.96.13.7563.
2. Shin, Chan Soo, and Hwa Young Cho. "Bone Remodeling and Mineralization." *Journal of Korean Society of Endocrinology*, vol. 20, no. 6, 2005, p. 543., doi:10.3803/jkes.2005.20.6.543.

*view further references for this research in the academic paper provided